REMARKS

I. Status of Claims

Claims 1, 4, 7-11, 15 and 19-31 are pending in this application. Claims 19-31 are under active examination. With this response, claims 1, 4, 7-11, 15, 19-21, and 25-31 are amended. Claims 22-24 are canceled and new claims 32-52 are added. Support for the amendments and new claims can be found in the specification as filed, including original claims. For example, support can be found at page 1, lines 27-28 (BCMA); page 8, lines 8-1 (80, 85, and 90% sequence identity); page 7, lines 25-26 (amino acids 1 to 51 of SEQ ID NO:1); page 5, lines 4-5 (amino acids 8-41 of SEQ ID NO:1); page 4, lines 20-21 (chimeric molecules); page 12, lines 10-28 (soluble forms of BCMA); page 4, lines 21-23 (chimeric molecules comprising an Fc domain); page 17, lines 20-31 (BAFF binding); page 11, lines 22-28 (BCMA fragments); and page 12, lines 13-17 (removal of the transmembrane domain). Applicants reserve the right to pursue subject matter not covered by the currently pending claims in one or more later filed applications.

II. Restriction/Election

Applicants affirm election of the claims of Group IV (claims 19-21). Claims 22-31 (presented in the Amendment of December 17, 2004) and new claims 32-52 are also drawn to the elected subject matter and Applicants request that these claims be examined with the claims of Group IV. Applicants note that the pending Office Action states that "claims 19-21 are under examination" (page 2, emphasis added), which

appears to be a typographical error, in view of the Examiner's reference to claims 19-31 throughout the Office Action.

III. Oath/Declaration

The Examiner has objected to the oath or declaration as defective because it allegedly has not been signed by inventor Fabienne MacKay. Applicants respectfully submit that on May 15, 2002, in response to a Notice to File Missing Parts, three Declarations were submitted: one containing the signatures of Jeffrey Browning, Christine Ambrose, and Jeffrey Thompson; one containing the signatures of Jurg Tschopp and Pascal Schneider, and one containing the signature of Fabienne MacKay. For the Examiner's convenience, Applicants attach copies of the three Declarations as filed on May 15, 2002, and the postcard, stamped by the PTO, confirming receipt of documents including "executed Declarations (3)."

IV. Information Disclosure Statement

Applicants attach a copy of reference BA (WO 99/12964) for consideration by the Examiner. A new Form PTO-SB-08 is enclosed.

V. Formal Matters

The Examiner has objected to the use of the terms "BAFF-R" and "BAFF" without defining these terms at their first appearance in the claims. Applicants have amended the claims to recite "BAFF" as an acronym for "B cell activating factor" and "BCMA" as an acronym for "B cell maturation protein." The specification uses the terms "BCMA"

and "BAFF-R" interchangeably. See, e.g., page 1, lines 27-28; page 3, lines 25-26; and page 7, lines 6-7. However, since the application was filed, the term "BAFF-R" has come to be used more commonly to refer to a distinct protein that also serves as a receptor to BAFF. Thus, Applicants have amended the claims to recite the term "BCMA" instead of "BAFF-R" so that they are consistent with the most current usage of these terms by those of skill in the art.

VI. Double Patenting

The Examiner has provisionally rejected claims 19-31 under the doctrine of obvious-type double patenting, in view of claims 106, 107, and 151 of copending Application No. 10/380,703 ("the '703 application"). The Examiner also cites claim 12 of Publication 2004/0072188. Applicants respectfully note that Publication 2004/0072188 corresponds to the '703 application, and thus regard these as a single rejection.

This rejection is improper. The Examiner bases the double patenting rejection on the false premise that "the BAFF-R sequence of SEQ ID NO:10 of the '703 application is 100% identical as compared with SEQ ID NO:1 recited in the instant claims." Office Action, at 6. These sequences are not identical or even 80% identical. The '703 application relates to a distinct, later discovered, receptor to BAFF that has come to be known in the art as BAFF-R. SEQ ID NO:10 of the '703 application, which corresponds to the amino acid sequence of human BAFF-R, is distinct from SEQ ID NO:1 recited in the instant claims, which corresponds to the amino acid sequence of human BCMA.

Accordingly, the two applications relate to clearly distinct subject matter and Applicants thus respectfully request that the double patenting rejection be withdrawn.

VII. 35 U.S.C. § 112, First Paragraph - Written Description

The Examiner has rejected claims 19, 20, 21, 23, 24, 26, and 27-31 under the written description requirement of 35 U.S.C. § 112, first paragraph. The Examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that the specification does not adequately describe the genus of BAFF-R [BCMA] polypeptides recited in the claims.

Without conceding the Examiner's position, Applicants have amended the claims to more clearly define the scope of the invention. Applicants respectfully submit that the claims, as amended, are fully supported by the specification. The polypeptides recited in the amended claims are clearly defined in structural terms (BCMA polypeptides comprising specific amino acid residues of SEQ ID NO:1, fragments thereof, or polypeptides that are 80, 85, or 90 percent identical thereto). Support for these structural limitations can be found throughout the specification and the original claims, including, e.g., Figure 1 and the Sequence Listing (defining SEQ ID NO:1); page 7, line 23 (amino acids 1 to 184 of SEQ ID NO:1); page 7, lines 25-26 (amino acids 1 to 51 of SEQ ID NO:1); and page 5, lines 4-5 (amino acids 8 to 41 of SEQ ID NO:1). Support

for fragments, including several representative species, can be found at page 7, line 10 to page 8, line 2, for example. Support for polypeptides that are 80, 85, or 90 percent identical to SEQ ID NO:1 and methods for determining percent identity can be found at page 8, lines 3-22, for example.

Furthermore, claims reciting percent identity or fragment language are also limited with respect to function ("binds to BAFF") in the amended claims. Support for this limitation, including a variety of assays for determining whether a particular polypeptide binds to BAFF, can be found in Examples 1-4 (page 17, line 20 to page 21, line 10).

These structural and functional limitations provide the skilled artisan with ample description of the claimed genus of polypeptides. The claimed polypeptides are structurally limited in that they must include a sequence at least 80% identical to amino acids 1 to 51 of SEQ ID NO:1 or a fragment thereof. Through a routine mathematical exercise, the skilled artisan could list every sequence that meets this limitation. Having thus comprehended the genus of polypeptides satisfying the structural limitation, verification of those species retaining the functional characteristic of binding to BAFF requires only routine application of assays that are well known in the art and described in the specification.

Furthermore, the specification and routine knowledge in the art provide guidance as to which fragments and sequence variants are likely to retain the functional limitation

of binding to BAFF. The specification discloses that BCMA may be isolated from a variety of sources, including murine or human tissue. In fact, the sequences of both mouse and human BCMA were known in the art (see attached GenBank database entries). The skilled artisan would know to compare these sequences to identify which amino acids are conserved between the homologs and thus more likely to be important for BCMA activity. Conversely, amino acids that vary between the mouse and human sequences indicate regions of the polypeptide that are more likely to tolerate variation from SEQ ID NO:1. An example of such an alignment, generated using the routine "Align 2 sequences" function of the BLAST program, is attached.

In summary, Applicants provide the reference sequence upon which the claimed polypeptides are based, the extent of variation that is permissible, assays for determining whether the required function is retained, and guidance as to which residues are likely to tolerate variation from the reference sequence. Applicants' disclosure would allow the skilled artisan to readily contemplate the claimed genus of polypeptides, and thus to conclude that Applicants were in possession of the invention as claimed.

VIII. 35 U.S.C. §112, First Paragraph - Enablement

The Examiner has rejected claims 19-31 under the enablement requirement of 35 U.S.C. §112, first paragraph, stating that the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with

these claims. While acknowledging enablement of a pharmaceutical composition comprising an isolated BAFF-R of SEQ ID NO:1 or a fragment comprising residues 1-51 of SEQ ID NO:1 that is capable of binding BAFF, the Examiner alleges that the specification does not enable "sequence variants, naturally occurring variants, allelic variants, mammalian homologues or percent variants thereof or fusions to an immunoglobulin per se." Office Action, at 9.

Without conceding the Examiner's position, Applicants have amended the claims to more clearly define the scope of the invention. The amended claims do not recite "sequence variants, naturally occurring variants, allelic variants, mammalian homologues or percent variants thereof or fusions to an immunoglobulin per se." As discussed above with regard to written description, the amended claims recite polypeptides limited with respect to structure (BCMA polypeptides comprising specific amino acid residues of SEQ ID NO:1, fragments thereof, and polypeptides that are 80, 85, or 90 percent identical thereto) and function ("capable of binding to BAFF"). Applicants respectfully submit that the claims, as amended, are fully enabled by the specification.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. United States v. Telectronics, Inc. , 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); In re Stephens, 188 USPQ 659 (CCPA 1976). The test for

enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 190 USPQ 214 (CCPA 1976), emphasis added. Non-critical features of the invention may be supported by a more general disclosure than those at the heart of the invention. In re Stephens, 180 USPQ 659 (CCPA 1976).

The Examiner has the initial burden of giving reasons, supported by the record as a whole, why the specification is not enabling. In re Angstadt, supra. In the present case, the Examiner has not met this burden. Although the Examiner may have demonstrated that some experimentation is necessary, doing so is not enough to shift the burden to applicants to prove that such experimentation is not undue. Id.

In support of the allegation that the specification does not enable any variant, derivative, or homolog of BAFF-R as represented by SEQ ID NO:1, the Examiner contends that "one of skill in the art would be reduced to merely randomly altering amino acid(s) which would lead to unpredictable results regarding the functional activity of the protein." The Examiner cites Rudinger et al. as evidence of the general unpredictability of the effects of sequence variation on protein function and Burgess et al. and Lazar et al. as evidence that "a single amino acid substitution . . . will often dramatically affect the biological activity of the protein." Office Action, at 10.

At the outset, Applicants note that Rudinger et al. was published in 1976, fully 23 years before the priority date of the present application, and is therefore not

representative of the state of the art at the relevant time. Moreover, Rudinger is not applicable here since there is no requirement for one skilled in the art to predict *a priori* the significance of any particular amino acid. On the contrary, in the present case (and as discussed above with regard to written description) the skilled artisan would know which amino acids are conserved, and thus more likely to be important for BCMA activity, given that human and mouse BCMA sequences were known.

Furthermore, the fact that Burgess et al. and Lazar et al suggest that a single point mutation may occasionally affect a function in unrelated proteins does not meet the burden of demonstrating that Applicants' disclosure is not enabling. The far more common observation is that function is retained despite sequence variation, even when a significant number of amino acids has been deleted or otherwise mutated. Thus, evidence that single amino acid substitutions can disrupt the function of other, unrelated proteins would not preclude the skilled artisan from expecting success in practicing the claimed invention. This is also supported by the prior art. See, e.g., Bowie et al., Science 247:1306-1310 (1990) (copy enclosed). At page 1306, lines 12-13, Bowie teaches that "proteins are surprisingly tolerant of amino acid substitutions". Bowie et al. cites as evidence a study carried out on the *lac* repressor. Of approximately 1500 single amino acid substitutions at 142 positions in this protein, about one-half of the substitutions were found to be "phenotypically silent": that is, had no noticeable effect on the activity of the protein (Bowie at page 1306, col. 2, lines 14-17). Presumably the

other half of the substitutions exhibited effects ranging from slight to complete abolishment of repressor activity. Thus, one can expect, based on Bowie et al.'s teachings, to find over half (and possibly well over half) of random substitutions in any given protein to result in proteins with full or nearly full activity.

These odds are far better than those at issue in In re Wands, 858 F.2d 731 (Fed. Cir. 1988), in which the court said that screening many hybridomas to find the few that fell within the claims was not undue experimentation. The question then is not whether it is possible to predict for each possible mutation whether it can be tolerated, but rather whether one of ordinary skill can produce, without undue experimentation, species in which the activity is not abolished. Based on Bowie et al.'s teachings, one would predict that even random substitution of residues in a protein will predictably result in a majority of the species having full or partial activity. Again, the test for enablement is not whether one could make polypeptides lacking the recited function (and thereby falling outside the scope of the claims), but whether one could make polypeptides that *have* the recited function, without undue experimentation. That standard is clearly met in this case.

In addition to generally expecting success in practicing the invention, the skilled artisan would know how to make and test mutant BCMA polypeptides using techniques conventional in the art. For example, Fersht, Structure and Mechanism in Protein

Science 425 (1999) (copy enclosed) states that "[t]here are simple rules, however, to produce mutants that have a chance of being analyzed simply."

Even if a nonfunctional variant exists, it does not prove a lack of enablement of the claim. Atlas Powder Co. v. E.I. duPont de Nemous & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. A variety of procedures that can be used to determine whether a polypeptide binds to BAFF is described in Examples 1-4 (page 17, line 20 to page 21, line 10). Additional screening methods are routine in the art. See, e.g., Kricka, Ligand-Binder Assays: Labels and Analytical Strategies 1-3 (1985) (copy enclosed). Considering these Examples and the level of skill and knowledge in the art, one skilled in the art would be able to make and use the BCMA proteins required to practice the claimed methods without undue experimentation. With these proteins in hand, Examples 8-14 (page 23, line 23 to page 36, line 7) provide ample guidance as to how to use the invention.

In conclusion, Applicants' disclosure and information known in the art would allow one skilled in the art to make and use the claimed invention without undue experimentation. The Examiner has not met the burden of establishing that undue

experimentation is required. Therefore, Applicants request that the enablement rejection be withdrawn.

IX. 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 19-31 as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter of the invention.

The Examiner objects to the recitation of the term "therapeutically effective amount," alleging that it is unclear what therapeutic effect is achieved. Without acquiescing to the Examiner's position, Applicants have amended claim 19 to recite "an amount of a BCMA polypeptide effective to inhibit B-cell growth or immunoglobulin production, or both." Applicants respectfully submit that the amended claim language is clear and unambiguous.

The Examiner objects to claims 20, 22, 23-26, and 31, alleging that the "fragment language" does not have clear and unambiguous basis in claim 19. Without acquiescing to the Examiner's position, Applicants have amended claims 19, 20, 22, 23-26, and 31. The preambles of these claims, as amended, refer to "an isolated BCMA polypeptide" without "fragment language," which is now confined to the bodies of the claims. Applicants respectfully submit that the amended dependency language is clear and unambiguous.

Applicants affirm that "having the ability to bind BAFF" is the intended meaning of "capable of binding BAFF." The claims now recite "an amino acid sequence that binds to BAFF" or "a fragment thereof that binds to BAFF."

Applicants respectfully submit that the amended claims particularly point out and distinctly claim the subject matter which Applicants regard as the invention, and request that the indefiniteness rejection be withdrawn.

X. Priority

The Examiner has denied Applicants' claim for domestic priority to 60/149,378, 60/181,684, and 60/183,536, alleging that these provisional applications do not provide adequate support under 35 U.S.C. §112 for claims 19-31. In support of this position, the Examiner states that each provisional document "does not have written description for the reasons set forth below and further does not enable pharmaceutical use of any BAFF-R [BCMA] polypeptide or fragment thereof."

Without conceding the Examiner's position with respect to the previously pending claims, Applicants respectfully request that the Examiner reconsider the priority date with regard to the amended claims. Support for the amended claims can be found throughout the priority documents. With respect to the earliest priority claim, for example, support for the amended claims can be found in Application Serial No. 60/149,378, including at least on page 2, lines 4-8; page 5, lines 1-14; page 6, lines 1-11; page 7, lines 15-31; page 8, lines 1-18; page 10, lines 8-19; page 11, 14-30; page

14, lines 15-28; page 15, lines 12-31; and page 16, lines 1-10. Accordingly, Applicants respectfully submit that the amended claims are entitled to the earliest claimed priority date, August 17, 1999, and request that the claims for priority under 35 U.S.C. §119(e) and 35 U.S.C. §120 be granted.

XI. 35 U.S.C. §102

Claims 19-21 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by U.S. Patent No. 5,969,102 ("the '102 patent"). Without comment as to the previously pending claims, Applicants submit that the '102 patent does not anticipate the amended claims, which describe BCMA polypeptides by reference to SEQ ID NO:1. As noted by the Examiner, the '102 patent relates to TACI. TACI is a distinct and separate BAFF receptor that is not at least 80% identical to SEQ ID NO:1 or fragments thereof. Accordingly, Applicants respectfully request that the rejection over the '102 patent be withdrawn.

Claims 19-31 have been rejected under 35 U.S.C. §102(a) (claims 22 and 25) and 35 U.S.C. §102(b) (claims 18-21, 23, 24, 26-31) as allegedly anticipated by WO/00/40716 ("the '716 application"). In view of the foregoing remarks with respect to priority, Applicants submit that the instant application is entitled to the earliest priority date of August 17, 1999. Thus, without comment as to the alleged anticipation of the amended claims by the teachings of the '716 application, Applicants submit that the

instant application predates the reference, which is only effective as of its July 13, 2000, publication date.

Claims 19-31 have been rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,475,987 ("the '987 patent"). In view of the foregoing remarks with respect to priority, Applicants submit that the instant application is entitled to the earliest priority date of August 17, 1999. Thus, without comment as to the allegation that the claims read on the teachings of the '987 patent, Applicants submit that the instant application predates the reference, which issued November 5, 2002 and was filed May 5, 2000 (without acquiescing as to the priority date to which the '987 patent is entitled, Applicants note that the Examiner states that this reference has the benefit of priority to May 1, 2000). Accordingly, Applicants respectfully request that the rejection over the '987 patent be withdrawn.

Claims 19-31 have been rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent Application Publication 2003/0148445 ("the '445 application"). In view of the foregoing remarks with respect to priority, Applicants submit that the instant application is entitled to the earliest priority date of August 17, 1999. Thus, without comment as to the allegation that the claims read on the teachings of the '445 application, Applicants submit that the instant application predates the reference, which was published on August 7, 2003 and was filed August 9, 2002 (without acquiescing as to the priority date to which the '445 application is entitled, Applicants

note that the Examiner states that this reference has the benefit of priority to May 1, 2000). Accordingly, Applicants respectfully request that the rejection over the '445 application be withdrawn.

XIV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that all outstanding rejections have been overcome. Accordingly, reconsideration of claims and expedited allowance are earnestly requested. The Examiner is urged to call the undersigned with any questions at (617) 452-1650.

Applicants believe that any fee required for the entry of this Amendment and Response is accounted for by the accompanying Petition for Extension of Time. However, in the event of an error, please grant any additional extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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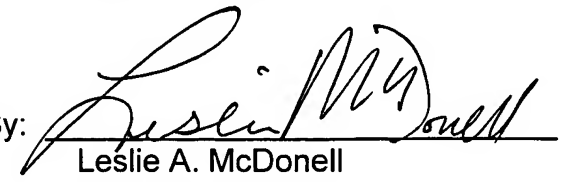
Dated: July 18, 2005

By: 
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